

**WHAT IS CLAIMED:**

1. An isolated nucleic acid molecule, comprising at least 14 contiguous nucleotides of an IDE gene allele corresponding to a sequence of 14 contiguous nucleotides that includes nucleotide position 122260 of SEQ ID NO:484, or the complement thereof, except that the nucleotide at position 122260 is replaced with a G, T or C, or is replaced with a C, A or G in a complementary sequence thereof.
2. The nucleic acid of claim 1, wherein the 14 contiguous nucleotides comprise a sequence of 5 contiguous nucleotides of SEQ ID NO:484, or the complement thereof, within the sequence of nucleotides from position 122256 to 122264, except that the nucleotide at position 122260 is replaced with a G, T or C, or is replaced with a C, A or G in a complementary sequence thereof.
3. The nucleic acid of claim 2, wherein the sequence of at least 14 contiguous nucleotides comprises a sequence of at least 14 contiguous nucleotides of SEQ ID NO:484, or the complement thereof, except that the nucleotide at position 122260 is replaced with a G, T or C, or is replaced with a C, A or G in a complementary sequence thereof.
4. The nucleic acid of claim 1, wherein the nucleotide at position 122260 is replaced with a G, or is replaced with a C in a complementary position thereof.
5. The nucleic acid molecule of claim 1, further comprising a coding nucleotide sequence operatively linked to a promoter.
6. An isolated nucleic acid molecule, comprising a coding nucleotide sequence operatively linked to a promoter, wherein the coding

nucleotide sequence is contained within a nucleotide sequence comprising a portion of an IDE gene allele that comprises a sequence of at least 14 contiguous nucleotides of an IDE gene allele but does not contain a contiguous sequence of a complete IDE gene allele,

- 5        wherein the sequence of at least 14 contiguous nucleotides corresponds to a sequence of 14 contiguous nucleotides that includes nucleotide position 122260 of SEQ ID NO:484, or the complement thereof, wherein the nucleotide at position 122260 is A, T, C or G; and  
      wherein the isolated nucleic acid includes sequence that is  
10    heterologous to the IDE gene allele.

7.    The isolated nucleic acid molecule of claim 6, wherein the sequence of at least 14 contiguous nucleotides comprises a sequence of 5 contiguous nucleotides of SEQ ID NO:484, or the complement thereof,  
15    within the sequence of nucleotides from position 122256 to 122264, wherein the nucleotide at position 122260 is A, T, C or G.

8.    The nucleic acid molecule of claim 7, wherein the sequence of at least 14 contiguous nucleotides comprises a sequence of at least 14  
20    contiguous nucleotides of SEQ ID NO:484, or the complement thereof, that comprises said nucleotide at position 122260.

9.    The nucleic acid molecule of claim 6, wherein the coding nucleotide sequence encodes a reporter molecule that is not an IDE  
25    protein.

10.   The nucleic acid molecule of claim 6, wherein the coding nucleotide sequence encodes an IDE protein.

- 30    11.   The nucleic acid molecule of claim 6, wherein the promoter comprises a promoter that is heterologous to the IDE gene.

12. The nucleic acid molecule of claim 6, wherein the promoter comprises an IDE gene promoter.

13. A vector comprising the nucleic acid molecule of claim 1.

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14. A cell comprising the nucleic acid molecule of claim 1, wherein the nucleic acid molecule is heterologous to the cell.

15. A non-human transgenic animal, comprising the nucleic acid molecule of claim 1, wherein the nucleic acid molecule is a transgenic element of the animal.

16. An isolated nucleic acid molecule, comprising at least 14 contiguous nucleotides of a KNSL1 gene allele corresponding to a sequence of 14 contiguous nucleotides that includes nucleotide position 15 41014 and/or 41015 of SEQ ID NO:347, or the complement thereof, wherein the sequence of 14 contiguous nucleotides comprises one or more nucleotides inserted between positions 41014 and 41015, or the complementary positions thereof.

20 17. The nucleic acid molecule of claim 16, wherein the 14 contiguous nucleotides comprise the nucleotide sequence AATTT, or the complement thereof, inserted between positions 41014 and 41015, or the complementary positions thereof.

25 18. The isolated nucleic acid molecule of claim 17, wherein the 14 contiguous nucleotides comprise a sequence of 5 contiguous nucleotides of SEQ ID NO: 347, or the complement thereof, within the sequence of nucleotides from position 41011 to 41018, except that between the nucleotides at positions 41014 and 41015 the sequence 30 AATTT is inserted, or the complement thereof is inserted in the complementary sequence.

19. The nucleic acid molecule of claim 18, wherein the sequence of at least 14 contiguous nucleotides comprises a sequence of at least 14 contiguous nucleotides of SEQ ID NO:347, or the complement thereof, that comprises said nucleotide position 41014 and/or 41015 and the  
5 nucleotide sequence AATTT inserted between nucleotide positions 41014 and 41015.

20. The nucleic acid molecule of claim 17, further comprising a coding nucleotide sequence operatively linked to a promoter.

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21. A vector comprising the nucleic acid molecule of claim 17.

22. A cell comprising the nucleic acid molecule of claim 17, wherein the nucleic acid molecule is heterologous to the cell.

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23. A non-human transgenic animal, comprising the nucleic acid molecule of claim 17, wherein the nucleic acid molecule is a transgenic element of the animal.

20 24. An isolated nucleic acid molecule, comprising a coding nucleotide sequence operatively linked to a promoter, wherein the coding nucleotide sequence is contained within a nucleotide sequence comprising a portion of a KNSL1 gene allele that comprises a sequence of at least 14 contiguous nucleotides of a KNSL1 gene allele but does not contain a  
25 contiguous sequence of a complete KNSL1 gene allele,

wherein the sequence of at least 14 contiguous nucleotides corresponds to a sequence of 14 contiguous nucleotides that includes nucleotide position 41014 and/or 41015 of SEQ ID NO:347, or the complement thereof, wherein the sequence does or does not contain one  
30 or more nucleotides inserted between nucleotide positions 41014 and 41015, or the complementary positions thereof.

25. The nucleic acid molecule of claim 24, wherein the sequence of at least 14 contiguous nucleotides that includes nucleotide position 41014 and/or 41015 of SEQ ID NO:347, or the complement thereof, does or does not contain the nucleotide sequence AATTT, or the  
5 complement thereof, inserted between nucleotide positions 41014 and 41015, or the complementary positions thereof.

26. The nucleic acid molecule of claim 24, wherein the sequence of at least 14 contiguous nucleotides comprises a sequence of 5  
10 contiguous nucleotides of SEQ ID NO:347, or the complement thereof, within the sequence of nucleotides from position 41010 to 41019, wherein the sequence does or does not contain one or more nucleotides inserted between nucleotide positions 41014 and 41015, or the complementary positions thereof.

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27. The nucleic acid molecule of claim 26, wherein the sequence of at least 14 contiguous nucleotides comprises a sequence of at least 14 contiguous nucleotides of SEQ ID NO:347, or the complement thereof, wherein the sequence does or does not contain one or more nucleotides  
20 inserted between nucleotide positions 41014 and 41015, or the complementary positions thereof.

28. The nucleic acid molecule of claim 24, wherein the coding nucleotide sequence encodes a reporter molecule that is not a KNSL1  
25 protein.

29. The nucleic acid molecule of claim 24, wherein the coding nucleotide sequence encodes a KNSL1 protein.

30. The nucleic acid molecule of claim 24, wherein the promoter  
30 comprises a promoter that is heterologous to a KNSL1 gene.

31. The nucleic acid molecule of claim 24, wherein the promoter comprises a KNSL1 gene promoter.

32. An isolated nucleic acid molecule, comprising at least 50  
5 contiguous nucleotides of a KNSL1 gene allele corresponding to a sequence of at least 50 contiguous nucleotides that includes nucleotide position 133354 and/or 133355 of SEQ ID NO:484, or the complement thereof, and one or more nucleotides inserted between nucleotides at positions 133354 and 133355, or the complementary positions thereof.

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33. The nucleic acid of claim 32, wherein the sequence of at least 50 contiguous nucleotides comprises a 6-, 7- or 8-bp poly-T sequence, or the complement thereof, inserted between nucleotides at positions 133354 and 133355, or the complementary positions thereof.

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34. The isolated nucleic acid molecule of claim 33, wherein the 50 contiguous nucleotides comprise a sequence of 5 contiguous nucleotides of SEQ ID NO: 484, or the complement thereof, within the sequence of nucleotides from position 133351 to 133358, except that  
20 between the nucleotides at positions 133354 and 133355 a 6-, 7-, or 8-bp polyT sequence is inserted, or the complement thereof is inserted in the complementary sequence.

35. The nucleic acid molecule of claim 34, wherein the sequence  
25 of at least 50 contiguous nucleotides comprises a sequence of at least 50 contiguous nucleotides of SEQ ID NO:484, or the complement thereof, that comprises said nucleotide position 133354 and/or 133355 and a 6-, 7-, or 8-bp polyT nucleotide sequence inserted between nucleotide positions 133354 and 133355.

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36. The nucleic acid molecule of claim 33, wherein a 7-bp polyT nucleotide sequence, or the complement thereof, is inserted between nucleotide positions 133354 and 133355, or the complementary positions thereof.

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37. The nucleic acid molecule of claim 33, further comprising a coding nucleotide sequence operatively linked to a promoter.

38. An isolated nucleic acid molecule, comprising a coding  
10 nucleotide sequence operatively linked to a promoter, wherein the coding nucleotide sequence is contained within a nucleotide sequence comprising a portion of a KNSL1 gene allele that comprises a sequence of at least 50 contiguous nucleotides of a KNSL1 gene allele but does not contain a contiguous sequence of a complete KNSL1 gene allele,

15 wherein the sequence of at least 50 contiguous nucleotides corresponds to a sequence of 50 contiguous nucleotides that includes nucleotide position 133354 and/or 133355 of SEQ ID NO:484, or the complement thereof, wherein the sequence does or does not contain one or more nucleotides inserted between nucleotide positions 133354 and  
20 133355; and

wherein the isolated nucleic acid includes sequence that is heterologous to the KNSL1 gene allele.

39. The nucleic acid molecule of claim 38, wherein the sequence  
25 of 50 contiguous nucleotides that includes nucleotide position 133354 and/or 133355 of SEQ ID NO:484, or the complement thereof, does or does not contain a 6-, 7- or 8-bp polyT sequence inserted between nucleotide positions 133354 and 133355.

30 40. The isolated nucleic acid molecule of claim 38, wherein the sequence of at least 50 contiguous nucleotides comprises a sequence of



5 contiguous nucleotides of SEQ ID NO:484, or the complement thereof, within the sequence of nucleotides from position 133350 to 133359, wherein the sequence does or does not contain one or more nucleotides inserted between nucleotide positions 133354 and 133355.

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41. The nucleic acid molecule of claim 40, wherein the sequence of at least 50 contiguous nucleotides comprises a sequence of at least 50 contiguous nucleotides of SEQ ID NO:484, or the complement thereof, that comprises said nucleotide at position 133354 and/or 133355 and  
10 does or does not contain one or more nucleotides inserted between nucleotide positions 133354 and 133355.

42. The nucleic acid molecule of claim 38, wherein the coding nucleotide sequence encodes a reporter molecule that is not a KNSL1  
15 protein.

43. The nucleic acid molecule of claim 38, wherein the coding nucleotide sequence encodes a KNSL1 protein.

20 44. The nucleic acid molecule of claim 38, wherein the promoter comprises a promoter that is heterologous to a KNSL1 gene.

45. The nucleic acid molecule of claim 38, wherein the promoter comprises a KNSL1 gene promoter.

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46. A vector comprising the nucleic acid molecule of claim 33.

47. A cell comprising the nucleic acid molecule of claim 33, wherein the nucleic acid molecule is heterologous to the cell.

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48. A non-human transgenic animal, comprising the nucleic acid molecule of claim 33, wherein the nucleic acid molecule is a transgenic element of the animal.

5        49. An isolated nucleic acid molecule, comprising at least 50  
contiguous nucleotides of a KNSL1 gene allele corresponding to a  
sequence of at least 50 contiguous nucleotides that includes nucleotide  
position 133354 of SEQ ID NO:484, or the complement thereof, except  
that the nucleotide at position 133354, or the complementary position  
10 thereof, is deleted.

50. The nucleic acid molecule of claim 49, wherein the 50  
contiguous nucleotides comprise a sequence of 5 contiguous nucleotides  
of SEQ ID NO:484, or the complement thereof, within the sequence of  
15 nucleotides from position 133351 to 133357, except that the nucleotide  
at position 133354, or the complementary position thereof, is deleted.

51. The nucleic acid molecule of claim 50, wherein the sequence  
of at least 50 contiguous nucleotides comprises a sequence of at least 50  
20 contiguous nucleotides of SEQ ID NO: 484, or the complement thereof,  
except that the nucleotide at position 133354, or the complementary  
position thereof, is deleted.

52. An isolated nucleic acid molecule, comprising a coding  
25 nucleotide sequence operatively linked to a promoter, wherein the coding  
nucleotide sequence is contained within a nucleotide sequence comprising  
a portion of a KNSL1 gene allele that comprises a sequence of at least 14  
contiguous nucleotides of a KNSL1 gene allele but does not contain a  
contiguous sequence of a complete KNSL1 gene allele,  
30 wherein the sequence of at least 14 contiguous nucleotides  
corresponds to a sequence of 14 contiguous nucleotides that includes

nucleotide position 132370 of SEQ ID NO:484, or the complement thereof, wherein the nucleotide at position 132370 is A, T, C or G; and wherein the isolated nucleic acid includes sequence that is heterologous to the KNSL1 gene allele.

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53. The isolated nucleic acid molecule of claim 52, wherein the sequence of at least 14 contiguous nucleotides comprises a sequence of 5 contiguous nucleotides of SEQ ID NO:484, or the complement thereof, within the sequence of nucleotides from position 132366 to 132374, wherein the nucleotide at position 132370 is A, T, C or G.

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54. The nucleic acid molecule of claim 53, wherein the sequence of at least 14 contiguous nucleotides comprises a sequence of at least 14 contiguous nucleotides of SEQ ID NO:484, or the complement thereof, that comprises said nucleotide at position 132370.

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55. The nucleic acid molecule of claim 52, wherein the nucleotide at position 132370 is A, or is T in the complementary position thereof.

20

56. The nucleic acid molecule of claim 52, wherein the coding nucleotide sequence encodes a reporter molecule that is not a KNSL1 protein.

25

57. The nucleic acid molecule of claim 52, wherein the coding nucleotide sequence encodes a KNSL1 protein.

58. The nucleic acid molecule of claim 52, wherein the promoter comprises a promoter that is heterologous to the KNSL1 gene.

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59. The nucleic acid molecule of claim 52, wherein the promoter comprises a KNSL1 gene promoter.

60. A vector comprising the nucleic acid molecule of claim 52.

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61. A cell comprising the nucleic acid molecule of claim 52, wherein the nucleic acid molecule is heterologous to the cell.

62. A non-human transgenic animal, comprising the nucleic acid molecule of claim 52, wherein the nucleic acid molecule is a transgenic element of the animal.

63. A primer, probe or antisense nucleic acid molecule, comprising a sequence of nucleotides that specifically hybridizes adjacent to, or at, a polymorphic region of a KNSL1 or an IDE gene allele corresponding to:

- 15
- (a) a region that includes position 41014 and/or 41015 of SEQ ID NO:347, or the complementary positions thereof, of a KNSL1 gene allele, or
  - 20 (b) a region that includes position 133354 and/or 133355 of SEQ ID NO:484, or the complementary positions thereof, of a KNSL1 gene allele, or
  - (c) a region that includes position 122260 of SEQ ID NO:484, or the complementary position thereof, of an IDE gene allele.

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64. The primer, probe or antisense nucleic acid molecule of claim 63, wherein the sequence of nucleotides specifically hybridizes adjacent to, or at, a sequence of nucleotides, or the complement thereof, of SEQ ID NO:347.

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65. The primer, probe or antisense nucleic acid molecule of claim 64, wherein the sequence of nucleotides specifically hybridizes adjacent to, or at, a sequence of nucleotides, or the complement thereof, that includes the nucleotide at position 41014 and/or 41015 of SEQ ID NO:347 and contains the nucleotide sequence AATTT, or the complement thereof, inserted between positions 41014 and 41015, or the complementary positions thereof.

66. The primer, probe or antisense nucleic acid molecule of claim 63, wherein the sequence of nucleotides specifically hybridizes adjacent to, or at, a sequence of nucleotides, or the complement thereof, comprising a sequence of 5 contiguous nucleotides of SEQ ID NO:347, within the sequence of nucleotides from position 41011 to 41018, wherein the sequence contains the sequence AATTT, or the complement thereof, inserted between the nucleotides at positions 41014 and 41015, or the complementary positions thereof.

67. The primer, probe or antisense nucleic acid molecule of claim 66, wherein the sequence of nucleotides contains at least 14 nucleotides but less than 1000 nucleotides.

68. The primer, probe or antisense nucleic acid molecule of claim 63, wherein the sequence of nucleotides specifically hybridizes adjacent to, or at, a sequence of nucleotides, or the complement thereof, of SEQ ID NO:484.

69. The primer, probe or antisense nucleic acid molecule of claim 68, wherein the sequence of nucleotides specifically hybridizes adjacent to, or at, a sequence of nucleotides, or the complement thereof, that includes the nucleotide at position 133354 and/or 133355 of SEQ ID NO:484 and does or does not contain a 6-, 7- or 8-bp polyT sequence, or

the complement thereof, inserted between positions 133354 and 133355, or the complementary positions thereof.

70. The primer, probe or antisense nucleic acid molecule of claim 5 63, wherein the sequence of nucleotides specifically hybridizes adjacent to, or at, a sequence of nucleotides, or the complement thereof, comprising a sequence of 5 contiguous nucleotides of SEQ ID NO:484, within the sequence of nucleotides from position 133351 to 133359, wherein the sequence does or does not contain a 6-, 7- or 8-bp polyT 10 sequence, or the complement thereof, inserted between the nucleotides at positions 133354 and 133355, or the complementary positions thereof.

71. The primer, probe or antisense nucleic acid molecule of claim 15 70, wherein the sequence of nucleotides contains at least 14 nucleotides but less than 1000 nucleotides.

72. The primer, probe or antisense nucleic acid molecule of claim 63, wherein the sequence of nucleotides specifically hybridizes adjacent 20 to, or at, a sequence of nucleotides, or the complement thereof, of SEQ ID NO:484.

73. The primer, probe or antisense nucleic acid molecule of claim 72, wherein the sequence of nucleotides specifically hybridizes adjacent 25 to, or at, a sequence of nucleotides, or the complement thereof, that includes a nucleotide at position 122260 of SEQ ID NO:484 wherein the nucleotide is an A or G, or is a T or C in the complementary sequence thereof.

74. The primer, probe or antisense nucleic acid molecule of claim 30 63, wherein the sequence of nucleotides specifically hybridizes adjacent

to, or at, a sequence of nucleotides, or the complement thereof,  
comprising a sequence of 5 contiguous nucleotides of SEQ ID NO:484,  
within the sequence of nucleotides from position 122256 to 122264,  
wherein the nucleotide at position 122260 is an A or a G, or is a T or a C  
5 in the complementary sequence thereof.

75. The primer, probe or antisense nucleic acid molecule of claim  
63, wherein the sequence of nucleotides contains at least 14 nucleotides  
but less than 1000 nucleotides.

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76. A method of detecting the presence or absence of a  
polymorphism of a KNSL1 gene, comprising determining the presence or  
absence of:

(a) a nucleotide insertion between nucleotides corresponding to  
15 nucleotide positions 41014 and 41015 of SEQ ID NO:347, or the  
complementary positions thereof, or

(b) a nucleotide insertion between nucleotides corresponding to  
nucleotide positions 133354 and 133355 of SEQ ID NO:484, or the  
complementary positions thereof, or

20 (c) a deletion of the nucleotide at a position corresponding to  
nucleotide position 133354 of SEQ ID NO:484, or at the complementary  
position thereof.

77. The method of claim 76, comprising determining the  
25 presence or absence of the nucleotide sequence AATTT, or the  
complement thereof, inserted between nucleotides corresponding to  
nucleotide positions 41014 and 41015 of SEQ ID NO:347, or the  
complementary positions thereof.

30 78. The method of claim 76, comprising determining the  
presence or absence of a polyT nucleotide sequence, or the complement

thereof, inserted between nucleotides corresponding to nucleotide positions 133354 and 133355 of SEQ ID NO:484, or the complementary positions thereof.

5           79. The method of claim 78, comprising determining the presence or absence of a 6-, 7-, or 8-bp polyT nucleotide sequence, or the complement thereof, inserted between nucleotides corresponding to nucleotide positions 133354 and 133355 of SEQ ID NO:484, or the complementary positions thereof.

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80. A method of detecting the presence or absence of a polymorphism of a gene, comprising determining the identity of a nucleotide at a position corresponding to nucleotide position 132370 of SEQ ID NO:484, or the complement thereof.

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81. A method of detecting the presence or absence of a polymorphism of a gene, comprising determining the identity of one or more nucleotides at one or more positions corresponding to nucleotide positions 122260, 121239, 120416, 120288, 80752 and 54795 of SEQ ID NO: 484, or the complementary positions thereof.

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82. The method of claim 81, wherein the identity of a nucleotide at a position corresponding to nucleotide position 122260 of SEQ ID NO:484, or the complement thereof, is determined.

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83. The method of claim 81, wherein the identity of one or more nucleotides at one or more positions corresponding to nucleotide positions 120416, 120288 and 80752 of SEQ ID NO: 484, or the complementary positions, thereof is (are) determined.

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84. The method of claim 83, wherein the identities of the nucleotides at each of the positions corresponding to nucleotide positions 120416, 120288 and 80752 of SEQ ID NO: 484, or the complementary positions, thereof are determined.

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85. The method of claim 81, wherein the identity of one or more nucleotides at one or more positions corresponding to nucleotide positions 121239, 120416 and 80752 of SEQ ID NO: 484, or the complementary positions, thereof is (are) determined.

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86. The method of claim 85, wherein the identities of the nucleotides at each of the positions corresponding to nucleotide positions 121239, 120416 and 80752 of SEQ ID NO: 484, or the complementary positions, thereof are determined.

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87. The method of claim 81, wherein the identity of one or more nucleotides at one or more positions corresponding to nucleotide positions 122260, 120416, 120288, 80752 and 54795 of SEQ ID NO: 484, or the complementary positions thereof, is (are) determined.

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88. The method of claim 87, wherein the identities of the nucleotides at each of the positions corresponding to nucleotide positions 122260, 120416, 120288, 80752 and 54795 of SEQ ID NO: 484, or the complementary positions thereof, are determined.

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89. The method of claim 80 or claim 81, wherein the identity of the nucleotide(s) is determined in nucleic acid obtained from an individual who has or exhibits a characteristic of a neurodegenerative disease or who has a family member who has a neurodegenerative disease.

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90. A method for assessing an individual's level of risk for developing a neurodegenerative disease or for determining the occurrence of a neurodegenerative disease in an individual, comprising:

5 assessing in a nucleic acid sample obtained from an individual the presence of one or more polymorphisms of chromosome 10 selected from the group consisting of:

(a) a nucleotide insertion between nucleotides corresponding to nucleotide positions 41014 and 41015 of SEQ ID NO:347, or the complementary positions thereof;

10 (b) a nucleotide insertion between nucleotides corresponding to nucleotide positions 133354 and 133355 of SEQ ID NO:484, or the complementary positions thereof; and

(c) a nucleotide at one or more positions corresponding to nucleotide positions 132370, 122260, 121239, 120416, 120288, 80752  
15 and 54795 of SEQ ID NO: 484, or the complementary positions thereof;  
wherein the presence of the polymorphism is indicative of risk for or protection against a neurodegenerative disease.

91. The method of claim 90, comprising detecting the presence  
20 or absence of a nucleotide insertion between nucleotides corresponding to nucleotide positions 41014 and 41015 of SEQ ID NO:347, or the complementary positions thereof.

92. The method of claim 91, wherein the nucleotide insertion  
25 comprises the nucleotide sequence AATTT, or the complement thereof.

93. The method of claim 90, comprising detecting the presence or absence of a nucleotide insertion between nucleotides corresponding to nucleotide positions 133354 and 133355 of SEQ ID NO:484, or the  
30 complementary positions thereof.

94. The method of claim 93, wherein the nucleotide insertion comprises a polyT nucleotide sequence, or the complement thereof.

95. The method of claim 94, wherein the nucleotide insertion is the nucleotide sequence TTTTTTT, or the complement thereof.

96. The method of claim 90, comprising assessing the presence of a polymorphism at one or more positions corresponding to nucleotide positions 132370, 122260, 121239, 120416, 120288, 80752 and 54795 of SEQ ID NO: 484, or the complementary positions thereof.

97. The method of claim 96, comprising assessing the presence of a polymorphism at a position corresponding to nucleotide position 122260 of SEQ ID NO:484, or the complementary position thereof.

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98. The method of claim 97, comprising assessing the presence of a G at a position corresponding to nucleotide position 122260 of SEQ ID NO:484, or a C at a position corresponding to the complementary position thereof.

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99. The method of claim 97, comprising assessing the presence of an A at a position corresponding to nucleotide position 122260 of SEQ ID NO:484, or a T at a position corresponding to the complementary position thereof.

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100. The method of claim 96, comprising assessing the presence of a polymorphism at a position corresponding to nucleotide position 132370 of SEQ ID NO:484, or the complementary position thereof.

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101. The method of claim 100, comprising assessing the presence of an A at a position corresponding to nucleotide position 132370 of SEQ

ID NO:484, or a T at a position corresponding to the complementary position thereof.

102. The method of claim 96, comprising assessing the presence  
5 of one or more of the following nucleotides:

(a) an A at a position corresponding to nucleotide position 121239 of SEQ ID NO:484, or a T at a position corresponding to the complementary position thereof;

(b) an A at a position corresponding to nucleotide position 120416  
10 of SEQ ID NO:484, or a T at a position corresponding to the complementary position thereof;

(c) a G at a position corresponding to nucleotide position 120288 of SEQ ID NO:484, or a C at a position corresponding to the complementary position thereof;

(d) an A at a position corresponding to nucleotide position 80752  
15 of SEQ ID NO:484, or a T at a position corresponding to the complementary position thereof; and

(e) a G at a position corresponding to nucleotide position 54795 of SEQ ID NO:484, or a C at a position corresponding to the complementary  
20 position thereof.

103. The method of claim 96, comprising assessing the presence of a polymorphism at each of the positions corresponding to nucleotide positions 120416, 120288 and 80752 of SEQ ID NO: 484, or the  
25 complementary positions thereof.

104. The method of claim 103, comprising assessing the presence of an A at a position corresponding to nucleotide position 120416 of SEQ ID NO:484, or a T at a position corresponding to the complementary  
30 position thereof; an A at a position corresponding to nucleotide position 120288 of SEQ ID NO:484, or a T at a position corresponding to the

complementary position thereof; and an A at a position corresponding to nucleotide position 80752 of SEQ ID NO:484, or a T at a position corresponding to the complementary position thereof.

5           105. The method of claim 96, comprising assessing the presence of a polymorphism at each of the positions corresponding to nucleotide positions 121239, 120416 and 80752 of SEQ ID NO: 484, or the complementary positions thereof.

10           106. The method of claim 105, comprising assessing the presence of a C at a position corresponding to nucleotide position 121239 of SEQ ID NO:484, or a G at a position corresponding to the complementary position thereof; an A at a position corresponding to nucleotide position 120416 of SEQ ID NO:484, or a T at a position corresponding to the  
15 complementary position thereof; and an A at a position corresponding to nucleotide position 80752 of SEQ ID NO:484, or a T at a position corresponding to the complementary position thereof.

          107. The method of claim 96, comprising assessing the presence  
20 of a polymorphism at each of the corresponding to nucleotide positions 122260, 120416, 120288, 80752 and 54795 of SEQ ID NO: 484, or the complementary positions thereof.

          108. The method of claim 107, comprising assessing the presence  
25 of a G at a position corresponding to nucleotide position 122260 of SEQ ID NO:484, or a C at a position corresponding to the complementary position thereof; an A at a position corresponding to nucleotide position 120416 of SEQ ID NO:484, or a T at a position corresponding to the complementary position thereof; a G at a position corresponding to  
30 nucleotide position 120288 of SEQ ID NO:484, or a C at a position corresponding to the complementary position thereof; and an A at a

position corresponding to nucleotide position 80752 of SEQ ID NO:484,  
or a T at a position corresponding to the complementary position thereof;  
and a G at a position corresponding to nucleotide position 54795 of SEQ  
ID NO:484, or a C at a position corresponding to the complementary  
5 position thereof.

109. The method of claim 107, comprising assessing the presence  
of an A at a position corresponding to nucleotide position 122260 of  
SEQ ID NO:484, or a T at a position corresponding to the complementary  
10 position thereof; an A at a position corresponding to nucleotide position  
120416 of SEQ ID NO:484, or a T at a position corresponding to the  
complementary position thereof; a G at a position corresponding to  
nucleotide position 120288 of SEQ ID NO:484, or a C at a position  
corresponding to the complementary position thereof; and an A at a  
15 position corresponding to nucleotide position 80752 of SEQ ID NO:484,  
or a T at a position corresponding to the complementary position thereof;  
and a G at a position corresponding to nucleotide position 54795 of SEQ  
ID NO:484, or a C at a position corresponding to the complementary  
position thereof.

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110. The method of any of claims 92, 95, 98, 101, 104, 106 and  
108 wherein the presence of the polymorphism is indicative of risk for a  
neurodegenerative disease.

25 111. The method of claim 99 or claim 109, wherein the presence  
of the polymorphism is indicative of protection against a  
neurodegenerative disease.

112. The method claim 90, wherein the neurodegenerative  
30 disease is Alzheimer's disease.

113. The method of claim 90, further comprising determining if the individual is homozygous for the polymorphism.

114. A method of screening for an agent that modulates the expression and/or activity of IDE, comprising:

assessing the effect of a test agent on the expression of a coding nucleotide sequence operatively linked to a promoter, wherein the coding nucleotide sequence is contained within a nucleotide sequence comprising at least a portion of the IDE gene that comprises a sequence of at least 14 contiguous nucleotides of an IDE gene allele,

wherein the sequence of at least 14 contiguous nucleotides corresponds to a sequence of at least 14 contiguous nucleotides that includes the nucleotide at position 122260 of SEQ ID NO:484, or the complement thereof, wherein the nucleotide at position 122260 is replaced with a G, T or C, or is replaced with a C, A or G in a complementary sequence thereof; and

identifying a test agent as an agent that modulates the expression and/or activity of IDE if it has an effect on expression of the coding nucleotide sequence.

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115. The method of claim 114, wherein the sequence of 14 contiguous nucleotides comprises a sequence of 5 contiguous nucleotides of SEQ ID NO:484, or the complement thereof, within the sequence of nucleotides from position 122256 to 122264, except that the nucleotide at position 122260 is replaced with a G, T or C, or is replaced with a C, A or G in the complement thereof.

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116. The method of claim 115, wherein the sequence of 14 contiguous nucleotides comprises a sequence of at least 14 contiguous nucleotides of SEQ ID NO:484, or the complement thereof, except that

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the nucleotide at position 122260 is replaced with a G, T or C, or is replaced with a C, A or G in the complement thereof.

117. The method of claim 114, wherein the nucleotide at position  
5 122260 is replaced with a G, or is replaced with a C in a complementary sequence thereof.

118. A method of screening for an agent that modulates the expression and/or activity of IDE, comprising:

10 assessing the effect of a test agent on the expression of a coding nucleotide sequence operatively linked to a promoter, wherein the coding nucleotide sequence is contained within a nucleotide sequence comprising a portion of the IDE gene that comprises a sequence of at least 14 contiguous nucleotides of an IDE gene allele but that is not a contiguous  
15 sequence of a complete IDE allele;

wherein, the sequence of at least 14 contiguous nucleotides corresponds to a sequence of at least 14 contiguous nucleotides that includes the nucleotide at position 122260 of SEQ ID NO:484, or the complement thereof; and

20 identifying a test agent as an agent that modulates the expression and/or activity of IDE if it has an effect on expression of the coding nucleotide sequence.

119. The method of claim 118, wherein the sequence of at least  
25 14 contiguous nucleotides comprises a sequence of 5 contiguous nucleotides of SEQ ID NO: 484, or the complement thereof, within the sequence of nucleotides from position 122256 to 122264.

120. The method of claim 119, wherein the sequence of 14  
30 contiguous nucleotides comprises a sequence of at least 14 contiguous nucleotides of SEQ ID NO:484, or the complement thereof.

121. The method of claim 118, wherein the coding nucleotide sequence, promoter and portion of the IDE gene are contained in a nucleotide sequence that includes sequence that is heterologous to the IDE gene.

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122. The method of claim 114, wherein the coding sequence of nucleotides encodes an IDE protein or a reporter molecule.

123. The method of claim 114, wherein assessing comprises  
10 assessing the effect on expression of the coding sequence of nucleotides in a cell that comprises the coding sequence of nucleotides operatively linked to a promoter and contained within a nucleotide sequence comprising the portion of the IDE gene.

15 124. The method of claim 114, wherein assessing comprises assessing the effect on expression of the coding sequence of nucleotides in a non-human animal that comprises the coding sequence of nucleotides operatively linked to a promoter and contained within a nucleotide sequence comprising the portion of the IDE gene.

20

125. The method of claim 123, wherein the cell is a recombinant cell.

126. The method of claim 124, wherein the animal is a non-  
25 human transgenic animal.

127. The method of claim 123, wherein the coding sequence operatively linked to a promoter and contained within a nucleotide sequence comprising the portion of the IDE gene is heterologous to the  
30 cell.

128. The method of claim 124, wherein the coding sequence operatively linked to a promoter and contained within a nucleotide sequence comprising the portion of the IDE gene is a transgenic element in the transgenic animal.

5

129. The method of claim 114, wherein the promoter comprises an IDE gene promoter.

130. The method of claim 114, wherein a test agent is identified  
10 as an agent that modulates the expression and/or activity of IDE if it increases or decreases the level of expression of the coding sequence of nucleotides.

131. The method of claim 114, wherein a test agent is identified  
15 as an agent that modulates the expression and/or activity of IDE if it alters the level of expression of the coding sequence of nucleotides such that it is substantially similar to the level of expression of a coding sequence of nucleotides operatively linked to a promoter and contained within a nucleotide sequence comprising the portion of the IDE gene  
20 wherein the nucleotide at position 122260 is an A, or wherein the nucleotide at position 122260 is a T in the complementary sequence thereof.

132. The method of claim 114, wherein assessing comprises  
25 determining the effect on the level of mRNA encoding a protein encoded by the coding sequence of nucleotides or determining the effect on the level of protein or reporter molecule encoded by the coding sequence of nucleotides or determining the effect on the activity of a protein or reporter molecule encoded by the coding sequence of nucleotides.

30

133. A method of screening for an agent that modulates the expression and/or activity of KNSL1, comprising:

5 assessing the effect of a test agent on the expression of a coding nucleotide sequence operatively linked to a promoter, wherein the coding nucleotide sequence is contained within a nucleotide sequence comprising at least a portion of the KNSL1 gene that comprises a sequence of at least 50 contiguous nucleotides of a KNSL1 allele,

10 wherein the sequence of at least 50 contiguous nucleotides corresponds to a sequence of at least 50 contiguous nucleotides that includes nucleotide position 133354 and/or 133355 of SEQ ID NO:484, or the complement thereof, and one or more nucleotides inserted between nucleotides at positions 133354 and 133355, or the complementary positions thereof; and

15 identifying a test agent as an agent that modulates the expression and/or activity of KNSL1 if it has an effect on expression of the coding nucleotide sequence.

134. The method of claim 133, wherein the sequence of at least 50 contiguous nucleotides comprises a 6-, 7- or 8-bp polyT sequence, or  
20 the complement thereof, inserted between nucleotides at positions 133354 and 133355, or the complementary positions thereof.

135. The method of claim 133, wherein the sequence of at least 50 contiguous nucleotides comprises a sequence of 5 contiguous  
25 nucleotides of SEQ ID NO:484, or the complement thereof, within the sequence of nucleotides from position 133351 to 133358, and one or more nucleotides inserted between positions 133354 and 133355, or the complementary positions thereof.

30 136. The method of claim 135, wherein the sequence of at least 50 contiguous nucleotides comprises a sequence of at least 50

contiguous nucleotides of SEQ ID NO:484, or the complement thereof, and one or more nucleotides inserted between positions 133354 and 133355, or the complementary positions thereof.

5           137. A method of screening for an agent that modulates the expression and/or activity of KNSL1, comprising:

          assessing the effect of a test agent on the expression of a coding nucleotide sequence operatively linked to a promoter, wherein the coding nucleotide sequence is contained within a nucleotide sequence comprising  
10 a portion of the KNSL1 gene that comprises a sequence of at least 50 contiguous nucleotides of a KNSL1 gene allele but that is not a contiguous sequence of a complete KNSL1 allele;

          wherein the sequence of at least 50 contiguous nucleotides corresponds to a sequence of at least 50 contiguous nucleotides that  
15 includes nucleotide position 133354 and/or 133355, or the complement thereof, and contains or does not contain one or more nucleotides inserted between nucleotides 133354 and 133355; and

          identifying a test agent as an agent that modulates the expression and/or activity of KNSL1 if it has an effect on expression of the coding  
20 nucleotide sequence.

          138. The method of claim 137, wherein the sequence of at least 50 contiguous nucleotides comprises a sequence of 5 contiguous nucleotides of SEQ ID NO:484, or the complement thereof, within the  
25 sequence of nucleotides from position 133350 to 133359, and contains or does not contain one or more nucleotides inserted between nucleotides 133354 and 133355.

          139. The method of claim 137, wherein the sequence of at least  
30 50 contiguous nucleotides comprises a sequence of at least 50 contiguous nucleotides of SEQ ID NO:484, or the complement thereof,

and contains or does not contain one or more nucleotides inserted between nucleotides 133354 and 133355.

140. The method of claim 137, wherein the coding nucleotide  
5 sequence, promoter and portion of the KNSL1 gene are contained in a nucleotide sequence that includes sequence that is heterologous to the KNSL1 gene.

141. The method of claim 133, wherein the coding sequence of  
10 nucleotides encodes a KNSL1 protein or a reporter molecule.

142. The method of claim 133, wherein assessing comprises  
assessing the effect on expression of the coding sequence of nucleotides  
in a cell that comprises the coding sequence of nucleotides operatively  
15 linked to a promoter and contained within a nucleotide sequence comprising the said portion of the KNSL1 gene.

143. The method of claim 133, wherein assessing comprises  
assessing the effect on expression of the coding sequence of nucleotides  
20 in a non-human animal that comprises the coding sequence of nucleotides operatively linked to a promoter and contained within a nucleotide sequence comprising the said portion of the KNSL1 gene.

144. The method of claim 142, wherein the cell is a recombinant  
25 cell.

145. The method of claim 143, wherein the animal is a non-human transgenic animal.

30 146. The method of claim 142, wherein the coding sequence operatively linked to a promoter and contained within a nucleotide

sequence comprising the said portion of the KNSL1 gene is heterologous to the cell.

147. The method of claim 143, wherein the coding sequence  
5 operatively linked to a promoter and contained within a nucleotide sequence comprising the said portion of the KNSL1 gene is a transgenic element in the transgenic animal.

148. The method of claim 133, wherein the promoter comprises a  
10 KNSL1 gene promoter.

149. The method of claim 133, wherein a test agent is identified as an agent that modulates the expression and/or activity of KNSL1 if it increases or decreases the level of expression of the coding sequence of  
15 nucleotides.

150. The method of claim 133, wherein a test agent is identified as an agent that modulates the expression and/or activity of KNSL1 if it alters the level of expression of the coding sequence of nucleotides such  
20 that it is substantially similar to the level of expression of a coding sequence of nucleotides operatively linked to a promoter and contained within a nucleotide sequence comprising the said at least a portion of the KNSL1 gene wherein the sequence does not contain one or more nucleotides inserted between nucleotide positions 133354 and 133355.

25

151. The method of claim 150, wherein the one or more nucleotides inserted between nucleotide positions 133354 and 133355 is a 7-bp polyT sequence, or the complement thereof inserted between the complementary positions thereof.

30



152. The method of claim 133, wherein assessing comprises determining the effect on the level of mRNA encoding a protein encoded by the coding sequence of nucleotides or determining the effect on the level of protein or reporter molecule encoded by the coding sequence of  
5 nucleotides or determining the effect on the activity of a protein or reporter molecule encoded by the coding sequence of nucleotides.

153. A method of screening for an agent that modulates the expression and/or activity of KNSL1, comprising:  
10 assessing the effect of a test agent on the expression of a coding nucleotide sequence operatively linked to a promoter, wherein the coding nucleotide sequence is contained within a nucleotide sequence comprising at least a portion of the KNSL1 gene that comprises a sequence of at least 14 contiguous nucleotides of a KNSL1 gene allele,  
15 wherein the sequence of at least 14 contiguous nucleotides corresponds to a sequence of at least 14 contiguous nucleotides that includes nucleotide position 41014 and/or 41015 of SEQ ID NO:347, or the complement thereof, and one or more nucleotides inserted between nucleotides at positions 41014 and 41015, or the complementary  
20 positions thereof; and  
identifying a test agent as an agent that modulates the expression and/or activity of KNSL1 if it has an effect on expression of the coding nucleotide sequence.

25 154. The method of claim 153, wherein the sequence of at least 14 contiguous nucleotides comprises the nucleotide sequence AATTT, or the complement thereof, inserted between nucleotides at positions 41014 and 41015, or the complementary positions thereof.

30 155. The method of claim 153, wherein the sequence of at least 14 contiguous nucleotides comprises a sequence of 5 contiguous

nucleotides of SEQ ID NO:347, or the complement thereof, within the sequence of nucleotides from position 41011 to 41018, and one or more nucleotides inserted between positions 41011 and 41018, or the complementary positions thereof.

5

156. The method of claim 155, wherein the sequence of at least 14 contiguous nucleotides comprises a sequence of at least 14 contiguous nucleotides of SEQ ID NO:347, or the complement thereof, and one or more nucleotides inserted between positions 41011 and  
10 41018, or the complementary positions thereof.

157. A method of screening for an agent that modulates the expression and/or activity of KNSL1, comprising:

assessing the effect of a test agent on the expression of a coding  
15 nucleotide sequence operatively linked to a promoter, wherein the coding nucleotide sequence is contained within a nucleotide sequence comprising a portion of the KNSL1 gene that comprises a sequence of at least 14 contiguous nucleotides of a KNSL1 gene allele but that is not a contiguous sequence of a complete KNSL1 allele;

20 wherein the sequence of at least 14 contiguous nucleotides corresponds to a sequence of at least 14 contiguous nucleotides that includes nucleotide position 41014 and/or 41015, or the complement thereof, and contains or does not contain one or more nucleotides inserted between nucleotides 41014 and 41015; and

25 identifying a test agent as an agent that modulates the expression and/or activity of KNSL1 if it has an effect on expression of the coding nucleotide sequence.

158. The method of claim 157, wherein the sequence of at least  
30 14 contiguous nucleotides comprises a sequence of 5 contiguous nucleotides of SEQ ID NO:347, or the complement thereof, within the

sequence of nucleotides from position 41010 to 41019, and contains or does not contain one or more nucleotides inserted between nucleotides 41014 and 41015, or the complementary positions thereof.

5           159. The method of claim 158, wherein the sequence of at least 14 contiguous nucleotides comprises a sequence of at least 14 contiguous nucleotides of SEQ ID NO:347, or the complement thereof, and contains or does not contain one or more nucleotides inserted between nucleotides 41014 and 41015, or the complementary positions  
10 thereof.

          160. The method of claim 158, wherein the coding nucleotide sequence, promoter and portion of the KNSL1 gene are contained in a nucleotide sequence that includes sequence that is heterologous to the  
15 KNSL1 gene.

          161. The method of claim 153, wherein the coding sequence of nucleotides encodes a KNSL1 protein or a reporter molecule.

20           162. The method of claim 153, wherein assessing comprises assessing the effect on expression of the coding sequence of nucleotides in a cell that comprises the coding sequence of nucleotides operatively linked to a promoter and contained within a nucleotide sequence comprising the portion of the KNSL1 gene.

25           163. The method of claim 153, wherein assessing comprises assessing the effect on expression of the coding sequence of nucleotides in a non-human animal that comprises the coding sequence of nucleotides operatively linked to a promoter and contained within a nucleotide  
30 sequence comprising the portion of the KNSL1 gene.

164. The method of claim 162, wherein the cell is a recombinant cell.

165. The method of claim 163, wherein the animal is a non-  
5 human transgenic animal.

166. The method of claim 164, wherein the coding sequence  
operatively linked to a promoter and contained within a nucleotide  
sequence comprising the portion of the KNSL1 gene is heterologous to  
10 the cell.

167. The method of claim 165, wherein the coding sequence  
operatively linked to a promoter and contained within a nucleotide  
sequence comprising the said portion of the KNSL1 gene is a transgenic  
15 element in the transgenic animal.

168. The method of claim 153, wherein the promoter comprises a  
KNSL1 gene promoter.

20 169. The method of claim 153, wherein a test agent is identified  
as an agent that modulates the expression and/or activity of KNSL1 if  
increases or decreases the level of expression of the coding sequence of  
nucleotides.

25 170. The method of claim 153, wherein a test agent is identified  
as an agent that modulates the expression and/or activity of KNSL1 if it  
alters the level of expression of the coding sequence of nucleotides such  
that it is substantially similar to the level of expression of a coding  
sequence of nucleotides operatively linked to a promoter and contained  
30 within a nucleotide sequence comprising the said at least a portion of the

KNSL1 gene wherein the sequence does not contain one or more nucleotides inserted between nucleotide positions 41014 and 41015.

171. The method of claim 170, wherein the one or more  
5 nucleotides inserted between nucleotide positions 41014 and 41015 comprises the sequence AATTT, or the complement thereof inserted between the complementary positions thereof.

172. The method of claim 153, wherein assessing comprises  
10 determining the effect on the level of mRNA encoding a protein encoded by the coding sequence of nucleotides or determining the effect on the level of protein or reporter molecule encoded by the coding sequence of nucleotides or determining the effect on the activity of a protein or reporter molecule encoded by the coding sequence of nucleotides.

15

173. A method of screening for an agent that modulates the expression and/or activity of KNSL1, comprising:

assessing the effect of a test agent on the expression of a coding nucleotide sequence operatively linked to a promoter, wherein the coding  
20 nucleotide sequence is contained within a nucleotide sequence comprising at least a portion of the KNSL1 gene that comprises a sequence of at least 14 contiguous nucleotides of a KNSL1 gene allele,

wherein, the sequence of at least 14 contiguous nucleotides corresponds to a sequence of 14 contiguous nucleotides that includes  
25 nucleotide position 132370 of SEQ ID NO:484, or the complement thereof, except that the nucleotide at position 132370 is replaced with an A or is replaced with a T in the complement thereof; and

identifying a test agent as an agent that modulates the expression and/or activity of KNSL1 if it has an effect on expression of the coding  
30 nucleotide sequence.

174. A method of screening for an agent that modulates the expression and/or activity of KNSL1, comprising:

5 assessing the effect of a test agent on the expression of a coding nucleotide sequence operatively linked to a promoter, wherein the coding nucleotide sequence is contained within a nucleotide sequence comprising a portion of the KNSL1 gene that comprises a sequence of at least 14 contiguous nucleotides of a KNSL1 gene allele but that is not a contiguous sequence of a complete KNSL1 allele;

10 wherein the sequence of at least 14 contiguous nucleotides corresponds to a sequence of 14 contiguous nucleotides that includes nucleotide position 132370 of SEQ ID NO:484, or the complement thereof, wherein the nucleotide at position 132370 is A, G, T or C; and identifying a test agent as an agent that modulates the expression and/or activity of KNSL1 if it has an effect on expression of the coding  
15 nucleotide sequence.

175. The method of claim 173, wherein the sequence of at least 14 contiguous nucleotides comprises a sequence of 5 contiguous nucleotides of SEQ ID NO: 484, or the complement thereof, within the  
20 sequence of nucleotides from position 132366 to 132374, that comprises said nucleotide at position 132370.

176. The method of claim 173, wherein the sequence of at least 14 contiguous nucleotides is a sequence of at least 14 contiguous  
25 nucleotides of SEQ ID NO: 484, or the complement thereof, that comprises said nucleotide position at 132370.

177. The method of claim 174, wherein the coding nucleotide sequence, promoter and portion of the KNSL1 gene are contained in a  
30 nucleotide sequence that includes sequence that is heterologous to the KNSL1 gene.

178. The method of claim 173, wherein the coding sequence of nucleotides encodes a KNSL1 protein or a reporter molecule.

179. The method of claim 173, wherein assessing comprises  
5 assessing the effect on expression of the coding sequence of nucleotides in a cell that comprises the coding sequence of nucleotides operatively linked to a promoter and contained within a nucleotide sequence comprising the portion of the KNSL1 gene.

10 180. The method of claim 173, wherein assessing comprises assessing the effect on expression of the coding sequence of nucleotides in a non-human animal that comprises the coding sequence of nucleotides operatively linked to a promoter and contained within a nucleotide sequence comprising the said portion of the KNSL1 gene.

15 181. The method of claim 179, wherein the cell is a recombinant cell.

182. The method of claim 180, wherein the animal is a non-  
20 human transgenic animal.

183. The method of claim 179, wherein the coding sequence operatively linked to a promoter and contained within a nucleotide sequence comprising the said portion of the KNSL1 gene is heterologous  
25 to the cell.

184. The method of claim 180, wherein the coding sequence operatively linked to a promoter and contained within a nucleotide sequence comprising the said portion of the KNSL1 gene is a transgenic  
30 element in the transgenic animal.



185. The method of claim 173, wherein the promoter comprises a KNSL1 gene promoter.

186. The method of claim 173, wherein a test agent is identified  
5 as an agent that modulates the expression and/or activity of KNSL1 if increases or decreases the level of expression of the coding sequence of nucleotides.

187. The method of claim 173, wherein a test agent is identified  
10 as an agent that modulates the expression and/or activity of KNSL1 if it alters the level of expression of the coding sequence of nucleotides such that it is substantially similar to the level of expression of a coding sequence of nucleotides operatively linked to a promoter and contained within a nucleotide sequence comprising the said at least a portion of the  
15 KNSL1 gene wherein the nucleotide at position 132370 is a G or wherein the nucleotide at position 132370 is a C in the complementary sequence thereof.

188. The method of claim 173, wherein assessing comprises  
20 determining the effect on the level of mRNA encoding a protein encoded by the coding sequence of nucleotides or determining the effect on the level of protein or reporter molecule encoded by the coding sequence of nucleotides or determining the effect on the activity of a protein or reporter molecule encoded by the coding sequence of nucleotides.

25

189. A method of screening for an agent that modulates a biological event characteristic of a neurodegenerative disease, comprising:  
assessing the effect of a test agent on a biological event  
characteristic of a neurodegenerative disease exhibited by a cell or animal  
30 that comprises a sequence of nucleotides encoding IDE operatively linked to a promoter,

wherein the coding nucleotide sequence is contained within a nucleotide sequence comprising at least a portion of the IDE gene that comprises a sequence of at least 14 contiguous nucleotides of an IDE gene allele,

5        wherein the sequence of at least 14 contiguous nucleotides corresponds to a sequence of at least 14 contiguous nucleotides that includes the nucleotide at position 122260 of SEQ ID NO:484, or the complement thereof, wherein the nucleotide at position 122260 is replaced with a G, T or C, or is replaced with a C, A or G in a  
10       complementary sequence thereof; and

identifying a test agent as an agent that modulates a biological event characteristic of a neurodegenerative disease if it has an effect on the biological event characteristic of a neurodegenerative disease.

15       190. The method of claim 189, wherein the sequence of 14 contiguous nucleotides comprises a sequence of 5 contiguous nucleotides of SEQ ID NO:484, or the complement thereof, within the sequence of nucleotides from position 122256 to 122264, except that the nucleotide at position 122260 is replaced with a G, T or C, or is replaced with a C,  
20       A or G in the complement thereof.

191. The method of claim 190, wherein the sequence of 14 contiguous nucleotides comprises a sequence of at least 14 contiguous nucleotides of SEQ ID NO:484, or the complement thereof, except that  
25       the nucleotide at position 122260 is replaced with a G, T or C, or is replaced with a C, A or G in the complement thereof.

192. The method of claim 189, wherein the nucleotide at position 122260 is replaced with a G, or is replaced with a C in a complementary  
30       sequence thereof.

193. A method of screening for an agent that modulates a biological event characteristic of a neurodegenerative disease, comprising:

assessing the effect of a test agent on a biological event characteristic of a neurodegenerative disease exhibited by a cell or animal  
5 that comprises a sequence of nucleotides encoding IDE operatively linked to a promoter,

wherein the coding nucleotide sequence is contained within a nucleotide sequence comprising a portion of the IDE gene that comprises a sequence of at least 14 contiguous nucleotides of an IDE gene allele but  
10 that is not a contiguous sequence of a complete IDE allele, and

wherein, the sequence of at least 14 contiguous nucleotides corresponds to a sequence of at least 14 contiguous nucleotides that includes the nucleotide at position 122260 of SEQ ID NO:484, or the complement thereof; and

15 identifying a test agent as an agent that modulates a biological event characteristic of a neurodegenerative disease if it has an effect on the biological event characteristic of a neurodegenerative disease.

194. The method of claim 193, wherein the sequence of 14  
20 contiguous nucleotides comprises a sequence of 5 contiguous nucleotides of SEQ ID NO:484, or the complement thereof, within the sequence of nucleotides from position 122256 to 122264.

195. The method of claim 194, wherein the sequence of 14  
25 contiguous nucleotides comprises a sequence of at least 14 contiguous nucleotides of SEQ ID NO:484, or the complement thereof.

196. The method of claim 189, wherein the coding nucleotide sequence, promoter and portion of the IDE gene are contained in a  
30 nucleotide sequence that includes sequence that is heterologous to the IDE gene.

197. The method of claim 189, wherein the nucleotide sequence comprising a portion of the IDE gene is heterologous to the cell or animal.

198. The method of claim 189, wherein the cell is a recombinant  
5 cell.

199. The method of claim 189, wherein the animal is a non-human transgenic animal.

10 200. The method of claim 189, wherein the promoter comprises an IDE gene promoter.

201. The method of claim 189, wherein the neurodegenerative disease is Alzheimer's disease.

15

202. The method of claim 189, wherein the biological event is the level of an A $\beta$  peptide in the cell, extracellular medium or animal.

203. A method of screening for an agent that modulates a  
20 biological event characteristic of a neurodegenerative disease, comprising:  
assessing the effect of a test agent on a biological event  
characteristic of a neurodegenerative disease exhibited by a cell or animal  
that comprises a sequence of nucleotides encoding KNSL1 operatively  
linked to a promoter,

25 wherein the coding nucleotide sequence is contained within a  
nucleotide sequence comprising at least a portion of the KNSL1 gene that  
comprises a sequence of at least 50 contiguous nucleotides of a KNSL1  
gene allele, and

30 wherein the sequence of at least 50 contiguous nucleotides  
corresponds to a sequence of at least 50 contiguous nucleotides that  
includes nucleotide position 133354 and/or 133355 of SEQ ID NO:484,

or the complement thereof, and one or more nucleotides inserted between nucleotides at positions 133354 and 133355, or the complementary positions thereof; and

identifying a test agent as an agent that modulates a biological event characteristic of a neurodegenerative disease if it has an effect on the biological event characteristic of a neurodegenerative disease.

204. The method of claim 203, wherein the sequence of at least 50 contiguous nucleotides comprises a 6-, 7- or 8-bp polyT sequence, or the complement thereof, inserted between nucleotides at positions 133354 and 133355, or the complementary positions thereof.

205. The method of claim 203, wherein the sequence of at least 50 contiguous nucleotides comprises a sequence of 5 contiguous nucleotides of SEQ ID NO:484, or the complement thereof, within the sequence of nucleotides from position 133351 to 133358, and one or more nucleotides inserted between positions 133354 and 133355, or the complementary positions thereof.

206. The method of claim 205, wherein the sequence of at least 50 contiguous nucleotides comprises a sequence of at least 50 contiguous nucleotides of SEQ ID NO:484, or the complement thereof, and one or more nucleotides inserted between positions 133354 and 133355, or the complementary positions thereof.

207. The method of claim 203, wherein the sequence of at least 50 contiguous nucleotides comprises a 7-bp polyT sequence, or the complement thereof, inserted between nucleotides at positions 133354 and 133355, or the complementary positions thereof.

208. A method of screening for an agent that modulates a biological event characteristic of a neurodegenerative disease, comprising:

assessing the effect of a test agent on a biological event characteristic of a neurodegenerative disease exhibited by a cell or animal  
5 that comprises a sequence of nucleotides encoding KNSL1 operatively linked to a promoter,

wherein the coding nucleotide sequence is contained within a nucleotide sequence comprising a portion of the KNSL1 gene that comprises a sequence of at least 50 contiguous nucleotides of a KNSL1  
10 gene allele but that is not a contiguous sequence of a complete KNSL1 allele, and

wherein the sequence of at least 50 contiguous nucleotides corresponds to a sequence of at least 50 contiguous nucleotides that includes nucleotide position 133354 and/or 133355, or the complement  
15 thereof, and contains or does not contain one or more nucleotides inserted between nucleotides 133354 and 133355; and

identifying a test agent as an agent that modulates a biological event characteristic of a neurodegenerative disease if it has an effect on the biological event characteristic of a neurodegenerative disease.

20

209. The method of claim 208, wherein the sequence of at least 50 contiguous nucleotides comprises a sequence of 5 contiguous nucleotides of SEQ ID NO:484, or the complement thereof, within the sequence of nucleotides from position 133350 to 133359, and contains  
25 or does not contain one or more nucleotides inserted between nucleotides 133354 and 133355.

210. The method of claim 209, wherein the sequence of at least 50 contiguous nucleotides comprises a sequence of at least 50  
30 contiguous nucleotides of SEQ ID NO:484, or the complement thereof,

and contains or does not contain one or more nucleotides inserted between nucleotides 133354 and 133355.

211. The method of claim 203, wherein the coding nucleotide  
5 sequence, promoter and portion of the KNSL1 gene are contained in a nucleotide sequence that includes sequence that is heterologous to the KNSL1 gene.

212. The method of claim 203, wherein the nucleotide sequence  
10 comprising a portion of the KNSL1 gene is heterologous to the cell or animal.

213. The method of claim 203, wherein the cell is a recombinant  
cell.

15

214. The method of claim 203, wherein the animal is a non-human transgenic animal.

215. The method of claim 203, wherein the promoter comprises a  
20 KNSL1 gene promoter.

216. The method of claim 203, wherein the neurodegenerative disease is Alzheimer's disease.

25 217. The method of claim 203, wherein the biological event is the level of an A $\beta$  peptide in the cell, extracellular medium or animal.

218. A method of screening for an agent that modulates a biological event characteristic of a neurodegenerative disease, comprising:  
30 assessing the effect of a test agent on a biological event characteristic of a neurodegenerative disease exhibited by a cell or animal



that comprises a sequence of nucleotides encoding KNSL1 operatively linked to a promoter,

wherein the coding nucleotide sequence is contained within a nucleotide sequence comprising at least a portion of the KNSL1 gene that  
5 comprises a sequence of at least 14 contiguous nucleotides of a KNSL1 gene allele, and

wherein the sequence of at least 14 contiguous nucleotides corresponds to a sequence of at least 14 contiguous nucleotides that includes nucleotide position 41014 and/or 41015 of SEQ ID NO:347, or  
10 the complement thereof, and one or more nucleotides inserted between nucleotides at positions 41014 and 41015, or the complementary positions thereof; and

identifying a test agent as an agent that modulates a biological event characteristic of a neurodegenerative disease if it has an effect on  
15 the biological event characteristic of a neurodegenerative disease.

219. The method of claim 218, wherein the sequence of at least 14 contiguous nucleotides comprises the nucleotide sequence AATTT, or the complement thereof, inserted between nucleotides at positions 41014  
20 and 41015, or the complementary positions thereof.

220. The method of claim 218, wherein the sequence of at least 14 contiguous nucleotides comprises a sequence of 5 contiguous nucleotides of SEQ ID NO:347, or the complement thereof, within the  
25 sequence of nucleotides from position 41011 to 41018, and one or more nucleotides inserted between positions 41011 and 41018, or the complementary positions thereof.

221. The method of claim 220, wherein the sequence of at least  
30 14 contiguous nucleotides comprises a sequence of at least 14 contiguous nucleotides of SEQ ID NO:347, or the complement thereof,

and one or more nucleotides inserted between positions 41011 and 41018, or the complementary positions thereof.

222. A method of screening for an agent that modulates a biological event characteristic of a neurodegenerative disease, comprising:
- 5 assessing the effect of a test agent on a biological event characteristic of a neurodegenerative disease exhibited by a cell or animal that comprises a sequence of nucleotides encoding KNSL1 operatively linked to a promoter,
- 10 wherein the coding nucleotide sequence is contained within a nucleotide sequence comprising a portion of the KNSL1 gene that comprises a sequence of at least 14 contiguous nucleotides of a KNSL1 gene allele but that is not a contiguous sequence of a complete KNSL1 allele, and
- 15 wherein the sequence of at least 14 contiguous nucleotides corresponds to a sequence of at least 14 contiguous nucleotides that includes nucleotide position 41014 and/or 41015, or the complement thereof, and contains or does not contain one or more nucleotides inserted between nucleotides 41014 and 41015; and
- 20 identifying a test agent as an agent that modulates a biological event characteristic of a neurodegenerative disease if it has an effect on the biological event characteristic of a neurodegenerative disease.

223. The method of claim 222, wherein the sequence of at least 14 contiguous nucleotides comprises a sequence of 5 contiguous nucleotides of SEQ ID NO:347, or the complement thereof, within the sequence of nucleotides from position 41010 to 41019, and contains or does not contain one or more nucleotides inserted between nucleotides 41014 and 41015, or the complementary positions thereof.

30

224. The method of claim 223, wherein the sequence of at least 14 contiguous nucleotides comprises a sequence of at least 14 contiguous nucleotides of SEQ ID NO:347, or the complement thereof, and contains or does not contain one or more nucleotides inserted  
5 between nucleotides 41014 and 41015, or the complementary positions thereof.

225. The method of claim 218, wherein the coding nucleotide sequence, promoter and portion of the KNSL1 gene are contained in a  
10 nucleotide sequence that includes sequence that is heterologous to the KNSL1 gene.

226. The method of claim 218, wherein the nucleotide sequence comprising a portion of the KNSL1 gene is heterologous to the cell or  
15 animal.

227. The method of claim 218, wherein the cell is a recombinant cell.

20 228. The method of claim 218, wherein the animal is a non-human transgenic animal.

229. The method of 218, wherein the promoter comprises a KNSL1 gene promoter.

25

230. The method of claim 218, wherein the neurodegenerative disease is Alzheimer's disease.

231. The method of claim 218, wherein the biological event is the  
30 level of an A $\beta$  peptide in the cell, extracellular medium or animal.

232. A method of screening for an agent that modulates a biological event characteristic of a neurodegenerative disease, comprising:

assessing the effect of a test agent on a biological event characteristic of a neurodegenerative disease exhibited by a cell or animal  
5 that comprises a sequence of nucleotides encoding KNSL1 operatively linked to a promoter,

wherein the coding nucleotide sequence is contained within a nucleotide sequence comprising at least a portion of the KNSL1 gene that comprises a sequence of at least 14 contiguous nucleotides of a KNSL1  
10 gene allele, and

wherein the sequence of at least 14 contiguous nucleotides corresponds to a sequence of at least 14 contiguous nucleotides that includes nucleotide position 132370 of SEQ ID NO:484, or the complement thereof, except that the nucleotide at position 132370 is  
15 replaced with an A or is replaced with a T in the complement thereof; and

identifying a test agent as an agent that modulates a biological event characteristic of a neurodegenerative disease if it has an effect on the biological event characteristic of a neurodegenerative disease.

20 233. A method of screening for an agent that modulates a biological event characteristic of a neurodegenerative disease, comprising:

assessing the effect of a test agent on a biological event characteristic of a neurodegenerative disease exhibited by a cell or animal that comprises a sequence of nucleotides encoding KNSL1 operatively  
25 linked to a promoter,

wherein the coding nucleotide sequence is contained within a nucleotide sequence comprising a portion of the KNSL1 gene that comprises a sequence of at least 14 contiguous nucleotides of a KNSL1 gene allele but that is not a contiguous sequence of a complete KNSL1  
30 allele;

wherein the sequence of at least 14 contiguous nucleotides corresponds to a sequence of 14 contiguous nucleotides that includes nucleotide position 132370 of SEQ ID NO:484, or the complement thereof, wherein the nucleotide at position 132370 is A, G, T or C; and  
5 identifying a test agent as an agent that modulates a biological event characteristic of a neurodegenerative disease if it has an effect on the biological event characteristic of a neurodegenerative disease.

234. The method of claim 232, wherein the sequence of at least  
10 14 contiguous nucleotides comprises a sequence of 5 contiguous nucleotides of SEQ ID NO: 484, or the complement thereof, within the sequence of nucleotides from position 132366 to 132374, that comprises said nucleotide at position 132370.

15 235. The method of claim 232, wherein the sequence of at least 14 contiguous nucleotides is a sequence of at least 14 contiguous nucleotides of SEQ ID NO: 484, or the complement thereof, that comprises said nucleotide position at 132370.

20 236. The method of claim 233, wherein the coding nucleotide sequence, promoter and portion of the KNSL1 gene are contained in a nucleotide sequence that includes sequence that is heterologous to the KNSL1 gene.

25 237. The method of claim 232, wherein the nucleotide sequence comprising a portion of the KNSL1 gene is heterologous to the cell or animal.

238. The method of claim 232, wherein the cell is a recombinant  
30 cell.

239. The method of claim 232, wherein the animal is a non-human transgenic animal.

240. The method of claim 232, wherein the promoter comprises a  
5 KNSL1 gene promoter.

241. The method of claim 232, wherein the neurodegenerative disease is Alzheimer's disease.

10 242. The method of claim 232, wherein the biological event is the level of an  $A\beta$  peptide in the cell, extracellular medium or animal.